80* A randomised, double-blind, placebo-controlled parallel group study to investigate the safety and efficacy of two doses of tiotropium bromide (2.5 µg and 5 µg) administered once daily via the Respimat® device for 12 weeks in patients with cystic fibrosis

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Tiotropium bromide is an effective bronchodilator and may have additional potentially useful effects in CF. In this study 510 cystic fibrosis (CF) patients were randomized to 12 weeks treatment with 2.5 µg, 5 µg tiotropium or placebo. 138 patients ⩽11 years with a baseline mean FEV_1 percent predicted of 94% and 372 patients ⩾12 years with a mean baseline FEV_1 percent predicted of 69% were studied. Efficacy was shown in patients treated with tiotropium (2.5 µg and 5 µg) with statistically significant improvement (compared with placebo) for the co primary efficacy endpoints (percent predicted FEV_1 $AUC_{0–4h}$ response [2.5 µg – 2.94% {p = 0.001}; 5 µg – 3.39% {p = 0.0001}] at the end of Week 12 and pre-dose percent predicted FEV_1 response [2.5 µg – 2.24% {p = 0.0184}; 5 µg – 2.22% {0.0179}] at the end of Week 12). Volumetric changes in FEV_1 $AUC_{0–4h}$ at Week 12 were 90 mL for both 2.5 µg and 5 µg (p = 0.0004 and 0.0002, respectively). The overall safety profile of tiotropium was good with no unexpected safety findings. Reports of gastrointestinal events, particularly DIOS, occurred rarely. There were a total of 3 reports of DIOS (1 in the placebo group [0.6%]; 2 in the 5 µg group [1.1%]). This trial did not require withdrawing any medications and so tiotropium was tested on top of standard care. In additon, there was no upper limit for FEV_1 upon entry into the trial very often resulting in near normal lung function. The present study provides evidence of bronchodilator efficacy in CF patients treated with tiotropium (2.5 µg and 5 µg) once daily for 12 weeks. The safety and PK profiles are consistent with the patient population and do not demonstrate any cause for concern.

81* Inhaled L-arginine in patients with cystic fibrosis − a randomized controlled trial

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A single inhalation of nebulized L-arginine temporarily improves airway NO production and pulmonary function in patients with CF. However, L-arginine is also metabolized by arginase, an enzyme that forms ornithine and urea. Ornithine is the precursor of the polyamines which may contribute to airway remodeling.

Objective: To study safety and efficacy of repeated inhalations of nebulized L-arginine in CF patients.

Methods: A double-blind, randomized, placebo-controlled crossover treatment trial of twice daily inhalation of 500 mg L-arginine for two weeks compared to saline in 20 CF patients (NCT00405665 ClinicalTrials.gov).

Results: Nineteen patients completed the study. The inhalation of L-arginine was well tolerated. Inhaled L-arginine did not result in an increase in sputum neutrophil counts, Il-8 or neutrophil elastase. Exhaled NO (FENO) was significantly increased 30 and 60 min after the first inhalation of L-arginine ($p < 0.05$, respectively). FENO remained increased after 14 days of inhaled L-arginine (p = 0.03, paired t-test) but not placebo. FEV1 increased by an average of 65 ml after 14 days of L-arginine compared to −8 ml after placebo. This difference did not reach statistical significance. Sputum analyses revealed an increase in ornithine concentrations after inhaled L-arginine, but no change in sputum levels of the polyamine spermine (1.8 vs. 2.2 mmol/L, p = 0.7).

Conclusion: Repeated inhalation of L-arginine in this study was safe and well tolerated. Inhaled L-arginine resulted in an increase in NO production but no evidence for increased airway inflammation in CF patients.

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82* Microbiological and clinical response to tobramycin inhalation powder (TIP™) in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* (*Pa*) infection

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Objective: Aerosolized TOBI® has been used by CF patients for years. TIP™ has a similar clinical response to TOBI but with a shorter administration time, improving patient satisfaction. Questions remain about durability of the clinical response due to selection of resistant pathogens. We sought to assess the microbiological response to TIP vs TOBI in the EAGER trial.

Methods: 517 patients with chronic *Pa* infection received TIP (n = 308) or TOBI (n = 209) for 3 cycles (month on/month off). Resistance to tobramycin was based on parenteral breakpoint criteria (minimum inhibitory concentration [MIC] >8 µg/mL).

Results: At enrollment, 81% of patients had prior inhaled tobramycin use and 22% had resistant *Pa* isolates. The % of resistant isolates increased when on treatment, but decreased to baseline numbers during off-treatment periods. At study end, most isolates had a MIC 0.5–8 µg/mL (all biotypes). Despite the increase in MIC, at the end of Cycle 3, 89.4% of TIP patients had *Pa* isolates with a MIC ⩾30 times lower than the mean tobramycin sputum concentration post TIP-inhalation. *Pa* sputum density decreased during treatment periods; mean reduction (log_{10}) at the end of Cycle 3 was 1.61 (SD 2.03) in TIP- and 0.77 (SD 1.78) in TOBI-treated patients. Also, lung function (FEV_1% relative change) after 3 cycles improved in patients with resistant pathogens at baseline (mean change: TIP 1.4% and TOBI 3.0%, respectively).

Conclusion: Both TIP and TOBI reduce *Pa* density and improve lung function in CF patients irrespective of baseline MIC values.

83* Sinonasal inhalation of tobramycin in cystic fibrosis patients with *P. aeruginosa* colonization of the upper airways − results of a multicentric placebo-controlled pilot study

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Rationale: In CF sinonasal colonization with *P. aeruginosa* occurs primarily and as chronic persistent infection. Nasal inhalation with vibrating aerosols (Pari Sinus™) was shown to deposit drugs into paranasal sinuses. This is the first trial on nasal inhalation of vibrating antibiotic aerosol with the device applied in CF-patients with chronic pulmonary colonization and detection of *P. aeruginosa* in nasal lavages (NL).

Objectives: To evaluate primary endpoints and sample sizes for a principal study. Primary endpoint was *P. aeruginosa* quantification in NL. Secondary endpoints were ENT-related QoL assessed with the Sino-Nasal-Outcome-Test 20, otologic and renal tolerability.

Methods: Tobramycin 80 mg (Gernebcin™, 2 ml, 4 minutes per nostril) or NaCl 0.9% were inhaled once daily during 28 days. For the following 28 days all patients were offered Tobramycin therapy.

Results: 9 patients participated (6 Tobramycin, 3 NaCl 0.9%; 6m; mean age 22.3 yrs). Inhalation was well tolerated (Tobramycin serum levels <0.5 mg/l, stable Creatinine levels). *P. aeruginosa* quantity in NL decreased in 50% (3/6) of patients treated with Tobramycin but in none (0/3) treated with placebo (n.s.). Despite the small cohort nasal antibiotic inhalation lead to significant improvement of QoL compared to NaCl 0.9% (p = 0.036).

Conclusion: Sinonnasal inhalation of vibrating antibiotic aerosols appears to be a promising method for reduction of sinonasal symptoms and *P. aeruginosa* colonization.